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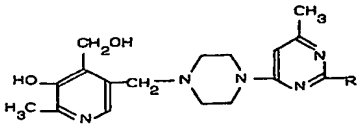
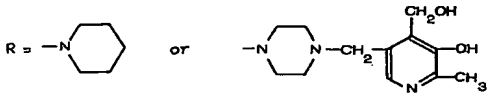
(54) Therapeutic pyrimidine derivatives

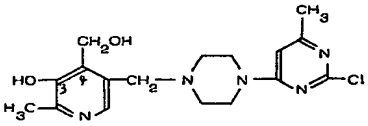
(57) The derivatives have the general formula



in which



and have anti-atheromatic activity. The derivatives may be prepared by reacting piperidine or piperazine RH is reacted with the corresponding chloride:



in which the 3–OH and 4–CH_2OH groups of the pyridoxine ring have been blocked. The reaction takes place under reflux in a polar solvent, and the blocking group is subsequently removed.

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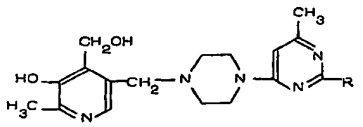
SPECIFICATION

Pyrimidine derivatives

DESCRIPTION

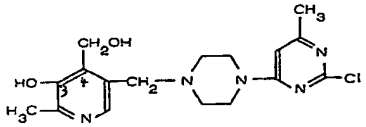
The invention relates to new complex pyrimidine derivatives which are especially interesting for their activity in the field of atheromas, to their preparation and the therapeutic compositions containing them.

The compounds according to this invention have the general formula:



in which R represents a piperidino radical or a 4-(2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl-methyl)-1- piperazinyl radical, and therapeutically acceptable salts thereof.

The above compounds can be prepared according to the invention by reacting, under reflux in a polar solvent, the piperdine or piperazine RH and the corresponding chloride:



in which the –OH and –CH_2OH groups in the 3 and 4 positions of the pyridoxine moiety have been previously blocked, using for example a blocking agent such as acetone,a nd then heating the compound thus obtained at from 70°C to 90°C to break the blocking of the said –OH and –CH_2OH groups. The compounds according to this invention and their therapeutically acceptable salts are especially interesting for their anti-atheromatic activity which, considered as a whole, is generally superior to that of standard reference compounds such as acetyl salicylic acid and its salts, ethyl *p*-chlorophenoxy- isobutyrate, nicotinic acid and its salts and 2,6-bis-(diethanol- amino)-4,8- dipiperidino- pyrimido-[5,4-d] pyrimidine.

Various experiments have shown a very favourable action of the compounds of the invention on:

(a) the vascular and parietal aspect of the atheromas (test of the oedema by ovalbumin and caragenin on rats; lowering of the capillary permeability on rats);

(b) the platelets aspect (platelets adhesivity *in vitro*; platelets agglutination *in vitro* by collagent, adrenalin and adenosine diphosphate; platelets agglutination *in vivo* on hamster's cheek pouch); and

(c) the fibrolipidic aspect (triton test on rats for triglycerids and cholesterol and experimental hyperlipemia and hypercholesterolemia tests on rabbits).

It has been noticed, for instance, in the case of the last tests on rabbits that the treated animals present a lowering of the total lipids below the figures found for control animals whereas animals having received only the hyperlipidic diet without treatment show a very important increase of lipemia. This does not occur for instance with ethyl *p*-chlorophenoxy isobutyrate.

In the triton test the protection given by the products of the invention is, for the same doses, 3 times better than the one given by ethyl *p*-chlorophenoxy- isobutyrate and 2,6-bis-(di- ethanolamino)-4,8-dipiperidino-pyrimido-[5,4-d] pyrimidine and is comparable to that given by nicotinic acid.

The following remarks apply to the products of both the following Examples.

The compound of Example 2 and its salts seem to be more active and have been found to act very satisfactorily in the same therapeutic field, as exemplified by the following experiments:

d) Action on the lipidic parameters of normal rats (method of K.M. BAGGALEY et. *al.*, J. of Medical Chemistry 1977 – *20*, No. 11, p. 1388–1393).

When administered to normal rats, the compound of Example 2 and its salts do not lower the cholesterol and total lipids rates, in contrast with the isopropyl ester of 2-methyl-2-[4-(4'- chlorobenzoyl)-phenoxy] propionic acid.

This is accordingly a strong advantage.

e) Action in dyslipemia provoked by fasting, on the rabbit. (Method of Ammerman C. B. *& al.* Am. J. Phys. 1961 – *200* p. 75–79).

Fasting induces, in rabbits, an increase of triglycerids, cholesterol and β-lipoproteins in the blood. In animals treated with the compound of Example 2 or its salts, the rates of these factors remain substantially normal whereas in animals treated with the isopropyl ester of 2-methyl-2-[4,(4'- chlorobenzoyl)- phenoxy] propionic acid, only the cholesterol and β-lipoproteins rates remain normal and the triglycerids rates are strongly increased (over the rates obtained for rabbits merely deprived of food).

TOXICITY

The toxicity of the compounds of Examples 1 and 2 has been researched *per os* on rats and mice: no deaths were recorded for mice at the maximum dose of 4 g/kg and 20% of deaths were recorded for rats at

the maximum dose of 3 g/kg. These values confirm the low toxicity of the compounds of the invention.

POSOLOGY – PRESENTATION

The invention also provides a therapeutic composition comprising at least one compound according to the invention in admixture with a therapeutically acceptable diluent or carrier.

For human therapy, the efficient doses *per os* are from 1.5 g to 10 g of active compound *per diem*.

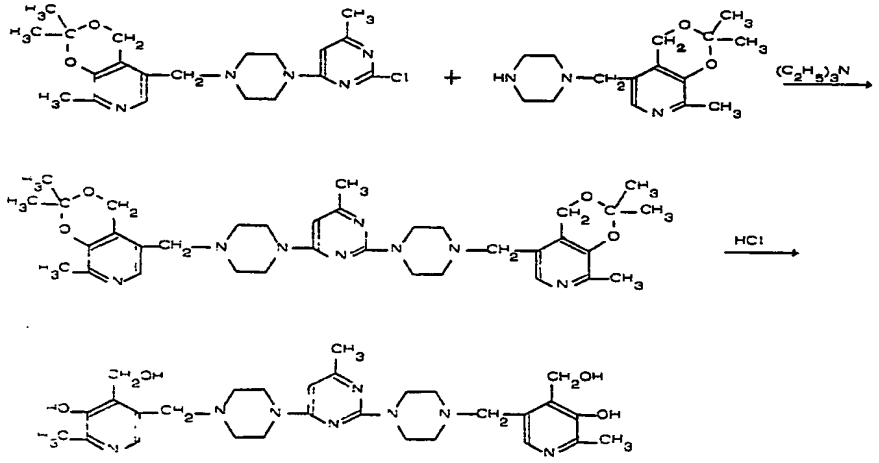
Preferred presentations comprise tablets and gelatine capsules containing 0.25 to 1 g of active compound.

The following Examples illustrate this invention.

Example 1:

Bis-2,4-[4-(2- methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)- 1-piperazinyl]-6-methyl- pyrimidine.

Reaction scheme:



Into a 10-litre reactor fitted with heating, cooling and stirring means, there were placed 277 g (1 mole) of 0,0'-isopropylidenyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-(N-piperazinyl- methyl)- pyridine, 3 litres of dry acetonitrile, 404 g (1 mole) of 2-chloro- 4-[4-(0,0'-isopropyli- denyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)- 1-piperazinyl]- 6-methyl- pyrimidine and 102 g (1 mole) of triethylamine. The mixture was stirred and refluxed for 40 hours and then cooled to 5°C.

A precipitate separated, was washed with diethyl ether and then with water free from chloride ions, and was dried to give 515 g (about 80% yield) of bis-2,4-[4-(0,0'- isopropylidenyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)- 1-piperazinyl]- 6-methyl- pyrimidine.

The 2-chloro-4-[4-(0,0'- isopropylidenyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)- 1-piperazinyl]- 6-methyl- pyrimidine used as starting material was obtained by reacting 0,0'-isopropyli- denyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-(N-piperazinyl- methyl)- pyridine with 2,4-dichloro- 6-methyl- pyridine in stoichiometric quantities in conditions similar to those described above excepts that the reflux was continued for only 20 hours.

The 2,4-dichloro- 6-methyl- pyridine was obtained by chlorination of methyluracil using phosphorus oxychloride.

The 0,0'-isopropyli- denyl- 2-methyl- 3-hydroxy- 4-hydroxymethy- 5-(N-piperazinyl- methyl)- pyridine was obtained by blocking the hydroxyl and hydroxymethyl groups at the 3- and 4- positions of pyridoxine by acetone in the presence of hydrochloric acid and reacting the resulting blocked pyridoxine with piperazine.

The bis-2,4-[4-(0,0'-isopropyli- denyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)- 1-piperazinyl]- 6-methyl- pyrimidine was treated with hydrochloric acid whilst stirring at about 80°C for 3 hours. This treatment broke the isopropylidene bridges and there was obtained 435 g (about 77% yield) of the desired product which was a white powder melting at about 240°C with decomposition. Analysis showed a good correspondence with the formula $C_{29}H_{40}N_8O_4$.

The compound was found to be insoluble in water, ethanol, chloroform and transcutanol at room temperature but soluble in dimethyl- sulphoxide in the same conditions.

The dimaleate and monocitrate salts were readily obtained by the usual routes. These salts were found to be soluble in water.

Example 2:

2-piperidino- 4-[4-(2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)- 1-piperazinyl]- 6-methyl- pyrimidine.

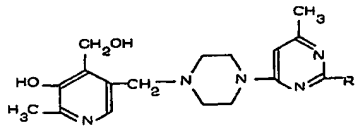
Example 1 was repeated except that the 0,0'-isopropylidenyl- 2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-(N-piperazinyl- methyl)- pyridine was replaced by 1 mole of piperidine. There was obtained the desired product which was a white powder melting at 208°C, in a yield of about 76%. Analysis showed a good correspondence with the formula $C_{22}H_{32}N_6O_2$. The compound was found to be insoluble at room temperature in water but soluble in chloroform, ethanol, transcutanol and dimethyl- sulphoxide.

The corresponding monocitrate is a white product melting at 118–121°C (Tottoli), fairly soluble in water at

room temperature if obtained by crystallization, or highly soluble in water if obtained by lyophilisation.

CLAIMS

1. A pyrimidine derivative of the general formula:

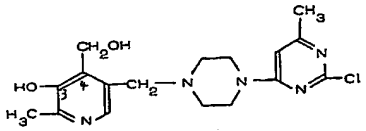


in which R represents a piperidino radical or a 4-(2-methyl- 3-hydroxy- 4-hydroxymethyl- 5-pyridyl- methyl)-1-piperazinyl radical or a therapeutically acceptable salt of such a derivative.

2. A pyrimidine derivative or a salt thereof according to claim 1, substantially as disclosed in Example 1 herein.

3. A pyrimidine derivative or a salt thereof according to claim 1, substantially as disclosed in Example 2 herein.

4. A process for the preparation of a pyrimidine derivative according to claim 1, comprising reacting, under reflux in a polar solvent, the piperidine or piperazine RH (in which R is as defined in claim 1) and the corresponding chloride:



in which the –OH and –CH_2OH groups in the 3 and 4 positions of the pyridoxine moiety have been previously blocked, then heating the compound thus obtained at from 70°C to 90°C to break the blocking of the said –OH and –CH_2OH groups.

5. A therapeutic composition comprising a compound according to claim 1 in admixture with a therapeutically acceptable diluent or carrier.

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